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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/690,880	10/22/2003	Nancy M. Lee	00010-004001	8369

26138 7590 01/08/2009

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ART UNIT	PAPER NUMBER
1636	

MAIL DATE	DELIVERY MODE
01/08/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/690,880	LEE ET AL.	
	Examiner	Art Unit	
	Jennifer Dunston, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-55,57,58,60-93,96 and 97* is/are pending in the application.

4a) Of the above claim(s) *1-48,50,65-78,80 and 89-93* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *49,51-55,57,58,60-64,79,81-88,96 and 97* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 October 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/22/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Exhibits I and II*.

DETAILED ACTION

The Examiner of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Jennifer Dunston, Art Unit 1636.

Any rejection of record in the previous office actions not addressed herein is withdrawn. New grounds of rejection are presented herein that were not necessitated by applicant's amendment of the claims since the office action mailed 4/22/2008. Therefore, this action is not final.

Receipt is acknowledged of an amendment, filed 10/22/2008, in which claim 59 was canceled, and claims 49, 57 and 79 were amended. Claims 1-55, 57, 58, 60-93, 96 and 97 are pending.

Election/Restrictions

Applicant elected Group III with traverse in the reply filed 6/21/2006. Applicant further elected the combination of biomarkers comprising SEQ ID NOs: 1, 2, 5, 15 and 16 (IL-8, COX-2, SAA1, PPAR-alpha and PPAR-gamma, respectively), and the oligonucleotide primers comprising SEQ ID NOs: 45 and 46, which amplify SEQ ID NO: 1; SEQ ID NOs: 47 and 48, which amplify SEQ ID NO: 2; SEQ ID NOs: 53 and 54, which amplify SEQ ID NO: 5; SEQ ID NOs: 73 and 74, which amplify SEQ ID NO: 15; and SEQ ID NOs: 75 and 76, which amplify SEQ ID NO: 16.

In the Office action mailed 9/11/2006, the Examiner withdrew the restriction requirement between Groups III and V. Although the restriction requirement mailed 5/5/2006 required an

election of a single invention, which is one combination of sequences, the record indicates that claims reading on less then the full combination of sequences have been examined. Thus, the claims will be considered as they read at least two sequences selected from the group consisting of SEQ ID NOs: 1, 2 and 5, as well as sequences selected from SEQ ID NOs: 15 and 16. The other combinations of sequences remain withdrawn.

Claims 1-48, 50, 65-78, 80 and 89-93 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 6/21/2006.

Claims 49, 51-55, 57, 58, 60-64, 79, 81-88, 96 and 97 are under consideration.

Information Disclosure Statement

Receipt of an information disclosure statement, filed on 10/22/2008, is acknowledged. The signed and initialed PTO 1449 has been mailed with this action.

Claim Objections

Claim 52 is objected to because of the following informalities: the phrase "copies of cDNA" should be deleted and the word "using" should be inserted after the word "comprises" to keep the language consistent with the amplifying step set forth in claim 49. Appropriate correction is required.

Claim 53 is objected to because of the following informalities: the phrase "copies of cDNA" should be deleted to keep the language consistent with the amplifying step set forth in claim 49. Appropriate correction is required.

Claim 60 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 60 is drawn to the method of claim 49, "where the step of obtaining a biological sample is by obtaining a sample of colorectal cells." However, claim 49 requires the step of "obtaining a biological colorectal sample from a subject." Because the colorectal sample of claim 49 is a biological sample, it will necessarily comprise cells. Accordingly, claim 60 fails to further limit claim 49.

Claim 96 is objected to because of the following informalities: the phrase "at least one cDNA" should be changed to "at least one biomarker" to be consistent with the terminology used in the preceding claims. Appropriate correction is required.

Claim 97 is objected to because of the following informalities: the phrase "at least one cDNA" should be changed to "at least one biomarker" to be consistent with the terminology used in the preceding claims. Appropriate correction is required.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined

application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 49, 51-53, 60, 61, 63 and 64 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 4-6 of copending Application No. 12/180,347 (hereinafter the '347 application). This is a new rejection.

Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed to methods for detection of colorectal cancer using RNA expression levels of the same biomarkers in the same types of samples, i.e., biological colorectal samples. Instant SEQ ID NOs: 45, 46, 47, 48, 53, 54, 73, 74, 75 and 76 correspond to SEQ ID NOs: 33, 34, 35, 36, 63, 64, 53, 54, 55 and 56, respectively, of the '347 application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 49, 54 and 60-62 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 104-107 of copending Application No. 11/827,894 (hereinafter the '894 application). This is a new rejection.

Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed to the determination of colorectal cancer in a subject, comprising measuring in biological colorectal samples the expression level of IL-8, and COX-2, which correspond to the biomarkers of instant SEQ ID NOs: 1 and 2.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 49, 51-55, 57, 58, 60-64, 79, 81-88, 96 and 97 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for (A) A method for assessing the risk of colorectal polyps and colorectal cancer in a subject, comprising (i) obtaining a biological colorectal sample from the subject; (ii) isolating cellular RNA from the sample; (iii) amplifying and quantifying RNA expression levels for SEQ ID NOs: 1 and 2; (iv) comparing the quantified expression levels of SEQ ID NOs: 1 and 2 in the sample from the subject to expression of SEQ ID NOs: 1 and 2 in normal control colorectal samples; and (v) determining an increased risk of colorectal polyps and colorectal cancer in the subject when at least one of SEQ

ID NOs: 1 and 2 is increased in expression in the sample from the subject as compared to the normal controls; and (B) A kit for assessing the risk of colorectal polyps and colorectal cancer, comprising oligonucleotides comprising the sequences set forth in SEQ ID NOs: 45, 46, 47 and 48, does not reasonably provide enablement for using the method for determination of colorectal polyps and colorectal cancer (i.e., diagnosis), or management of colorectal polyps and colorectal cancer, which includes estimating risk, early diagnosis, establishing prognosis, monitoring patient treatment, or detecting relapse; using any normal control sample as a comparison; using any change in expression levels to determine risk; using biomarkers selected from SEQ ID NOs: 5, 15 and 16. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. This rejection was made in the Office action mailed 4/22/2008; however, it has been rewritten to include and enabled scope.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art, the amount of experimentation necessary and the relative skill levels of those in the art. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the Invention: Claims 49, 51-55, 57, 58, 60-64, 96 and 97 are drawn to a method for "determination of colorectal cancer and colorectal polyps." The "determination of colorectal cancer and colorectal polyps" is reasonably construed as diagnosis of colorectal cancer and colorectal polyps. Dependent claim 57 requires the use of the gene expression levels to

identify a subject as a candidate for the management of colorectal cancer and colorectal polyps. To manage the polyps and cancer, one must be reliably diagnosed with the polyps and cancer. Dependent claim 58 indicates that the management of colorectal polyps and colorectal cancer encompasses risk assessment for unnamed events, early diagnosis, establishing prognosis, monitoring patient treatment for any treatment, and detecting relapse. The method comprises the following steps: (i) selecting a panel of biomarkers comprising at least two polynucleotides selected from the group consisting of SEQ ID NOs: 1, 2 and 5; (ii) obtaining a biological colorectal sample from a subject; (iii) isolating cellular RNA from the sample; (iv) amplifying and quantifying RNA expression levels for each biomarker in the panel comprising the at least two polynucleotides selected from the group consisting of SEQ ID NOs: 1, 2 and 5; and (v) comparing the quantified expression levels of each biomarker including the at least two polynucleotides in the sample to each biomarker expression level in a normal control, wherein a difference in the expression levels in the biological sample compared to the normal control is indicative of colorectal cancer and colorectal polyps. Claim 57 requires an increase in at least one biomarker of the selected biomarker panel in the sample compared to levels of the corresponding biomarkers from the normal control to identify the subject as a candidate for the management of colorectal cancer and colorectal polyps. Claim 96 limits the at least one cDNA of claim 57 to a cDNA comprising SEQ ID NO: 1. Claim 97 limits the at least one cDNA to a cDNA comprising SEQ ID NO: 2.

Dependent claims 51-55 further limit the step of amplifying and quantifying RNA expression levels. Claim 51 indicates that the panel of biomarkers further comprises at least one polynucleotide from SEQ ID NOs: 15 and 16. Claim 52 further limits the amplifying step to one

that uses at least two sets of primers chosen from (i) SEQ ID NO: 45 and 46; (ii) SEQ ID NO: 47 and 48; (iii) SEQ ID NO: 53 and 54; (iv) SEQ ID NO: 73 and 74; and (v) SEQ ID NO: 75 and 76. Claim 53 limits the step of amplifying to the use of enzymes and reagents for the preparation of cDNAs. Claim 54 limits the step of quantifying to further comprising labeling cDNA. Claim 55 limits the labeling to the inclusion of at least one chromophore.

Dependent claims 61-64 further limit the step of obtaining the sample. Claim 61 requires the step of obtaining to be minimally invasive or non-invasive. Claim 62 requires the minimally invasive step to be by use of a swab. Claim 63 requires the step of obtaining to be non-invasive, and claim 64 limits the non-invasive step to collection of a stool sample.

Claims 79 and 81-88 are drawn to a kit for the "determination of colorectal cancer and colorectal polyps." As discussed above, this term is construed as diagnosis of colorectal polyps and colorectal cancer. Claim 79 indicates that the kit comprises "at least one reagent that is used in the analysis of polynucleotide expression levels for a panel of biomarkers for colorectal cancer and colorectal polyps, where the panel comprises at least two polynucleotides listed in SEQ ID NOs: 1, 2; and 5; however the claim further defines the contents of the kit as oligonucleotides comprising the sequences set forth in SEQ ID NOs: 45, 46, 47, 48, 53 and 54, which amplify the biomarkers of SEQ ID NOs: 1, 2 and 5, and instructions. Claims 81-83 further limit the intended use of the kit with respect to the phrase "used in the analysis of polynucleotide expression levels for a panel of biomarkers for colorectal cancer and colorectal polyps." Claim 84 limits the primers to at least two sets of primers chosen from (i) SEQ ID NO: 45 and 46; (ii) SEQ ID NO: 47 and 48; (iii) SEQ ID NO: 53 and 54; (iv) SEQ ID NO: 73 and 74; and (v) SEQ ID NO; 75 and 76. Claim 85 further requires the kit to contain reagents for the preparation of cDNA. Claim 86

further requires the kit to contain a reagent that is used for the detection and quantitation of polynucleotides. Claim 87, limits the reagent of claim 86 to at least one chromophore. Claim 88 further requires the kit to contain consumable labware for at least one of sample collection, sample preparation or sample analysis.

The invention is complex in that it involves measuring a change in the level of RNA by amplification, such that a determination (diagnosis) of colorectal cancer and colorectal polyps is made. The present specification teaches that the two criteria for assessing the effectiveness of biomarkers are selectivity and sensitivity, where selectivity refers to the percentage of patients correctly diagnosed, and sensitivity is defined as the probability that the disease is detected at a curable stage (e.g., paragraph [0014]). The specification teaches that there is a difference between diagnosis and risk assessment. The specification states the following at paragraph [0029]:

> The difference between risk assessment and early detection is the degree of certainty regarding acquiring CRC. Biomarkers that are used for early detection confer less than 100% certainty of CRC within a time interval, whereas biomarkers used for early detection confer an almost 100% certainty of the onset of the disease within a specified time interval.

The nature of the invention is complex in that the claims require the use of RNA expression levels of the claimed biomarkers to diagnose colorectal polyps and colorectal carcinoma. Thus, the biomarkers must confer an almost 100% certainty of the onset of the disease within a specified time interval. The occurrence of adenomous polyps are a necessary, but not sufficient condition for an individual to later develop colorectal cancer; 90% of all preinvasive cancerous lesion are adenomous polyps or precursors, but not all individuals with adenomous polyps go on to later develop colorectal cancer (e.g., specification, paragraph

[0029]). The claims encompass the diagnosis of colorectal polyps and carcinoma. Given the relationship between polyps and carcinoma, the claims are essentially encompassing the diagnosis of colorectal carcinoma that has developed from polyps. The RNA expression levels must be able to distinguish between subjects with polyps only and those with polyps and cancer to diagnose cancer, because not every subject with polyps will have cancer.

Furthermore, the claims encompass the use of the diagnosis to perform risk assessment, early diagnosis, establishing prognosis, monitoring patient treatment, and detecting relapse of colorectal polyps and colorectal cancer. Thus one must know how to use the RNA expression levels of the claimed biomarkers as a class predictor for risk status, response to treatment, and presence or absence of relapse.

Breadth of the claims: The claims are broad in that they encompass the use of the method and kit for diagnosis, early diagnosis, establishing prognosis, monitoring patient treatment, and detecting relapse of colorectal polyps and colorectal cancer. The claims encompass the use of any normal control tissue, and do not limit the control tissue to the same tissue type as the test tissue, i.e., a biological colorectal sample. Furthermore, the claims encompass any difference in expression levels between the biological colorectal sample from the test subject and the normal control in that there may be any increase or decrease in expression of any two biomarkers selected from the group consisting of SEQ ID NOs: 1, 2 and 5 or at least two biomarkers selected from the group consisting of SEQ ID NOs: 1, 2 and 5 and at least one polynucleotide from SEQ ID NOs: 15 and 16.

Guidance of the specification/The existence of working examples: The specification discloses the use of a mouse multiple intestinal neoplasia (MIN) model to determine expression

differences between mouse MIN subjects comprising a chemically induced mutation in the APC gene and normal control littermates for which there was not aberration of the APC gene (page 5, paragraph 18). From these studies candidate genes were selected for study in human subjects; and from these studies with human samples, a disclosed panel of biomarkers was obtained. In one disclosed example, a panel of six biomarkers is used "as the basis for determination of CRC in human subjects" -- although the biomarkers were applied to samples obtained from patients known to have CRC and from individuals validated as normal controls (page 8, paragraph 27). The results are shown in Figure 2B for the panel of six markers, which include IL-8 (SEQ ID NO: 1), and COX2 (SEQ ID NO: 2), but does not include the markers of SEQ ID NO: 5, 15 or 16. In another example, multiple biopsy samples taken from one exemplary patient diagnosed with CRC showed differences in expression of three biomarkers (see paragraph bridging pages 9 and 10). However, the specification gives no indication of what such a difference in expression means for patient care management or for the discovery of therapeutic interventions. In the last example, the specification teaches that multiple biopsies (again from a single patient), taken over a 53 cm region of the colon, where able to "distinguish differences in the colon tissue for the patient" whereas the same biopsy samples were rendered normal by conventional histological analysis. The specification teaches that such results demonstrate a minimally invasive swabbing collection method from an area distant from a cancerous lesion is capable of indicating a "non-normal colon condition" (page 10, paragraph 32).

The specification does not provide a working example of the claimed method where a subject is diagnosed with colorectal polyps and colorectal cancer based upon the RNA expression levels of any two of the claimed biomarkers. Thus, the specification does not teach

the clinical selectivity and specificity of the test. The specification fails to teach how measurements of RNA expression can be used to manage patient care or to discover new therapeutic interventions. The specification lacks a single example of the use of expression levels of SEQ ID NOs: 1, 2 or 5 in combination to manage patient care or to discover new inventions for CRC or colorectal polyps.

The specification does not teach what differences in expression of SEQ ID NOs: 1, 2 or 5 can be used in order to perform early diagnosis, establishing a prognosis, monitoring patient treatment or detecting relapse. For example, does an increase or decrease in the level of SEQ ID NOs: 1, 2 or 5 indicate that a relapse is likely? How much of an increase or decrease is required for such a conclusion to be reached?

In addition, it is acknowledged in the specification that "there is a distinct difference between research on a specific a gene, its expression, protein product, and regulation, and understanding what genes are critical to include in a panel used to for the analysis of CRC that is useful in the management of patient care for the disease." (paragraph 0017) and the application demonstrates that there is substantial variation in expression levels of individual genes when compared with control sample (paragraph 0027), which necessitates the use of a panel of biomarkers for diagnostic validity. In spite of this, the application seeks to claim a method of using all panels of biomarkers comprising any two of SEQ ID NO: 1, 2 or 5 to determine colorectal cancer or colorectal polyps and seeks to claim a method wherein an increase in a single cDNA identifies a subject as a candidate for the management of colorectal cancer.

State of the prior art and level of predictability in the art: The "predictability or lack thereof" in the art refers to the ability of one skilled in the art to extrapolate the disclosed or

known results to the claimed invention. If one skilled in the art can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change within the subject matter to which that claimed invention pertains, then there is lack of predictability in the art. Accordingly, what is known in the art provides evidence as to the question of predictability.

The physiological art is recognized as unpredictable. (MPEP 2164.03.) In cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.

In the instant case, the specification teaches that "given the complexity of biological systems, discovery of panels useful in providing value in patient care management for CRC is in the nascent stage" (page 5, paragraph 16). The prior art supports this statement.

In general, the prior art teaches that there are many factors that need to be considered in order to develop a reliable genetic test. The art teaches that before a putative biomarker can be used as a surrogate endpoint it must be validated as such. Wagner (2002) *Dis. Markers* 18:41-46 acknowledges in the Abstract, "Putative biomarkers are typically identified because of a relationship to known or hypothetical steps in a pathophysiologic cascade. Biomarker discovery can also be effected by expression profiling experiment using a variety of array technologies and

related methods." However, Wagner cautions, "A rational basis for recommending the use of a putative biomarker does not guarantee the utility of the biomarker or its qualification as a surrogate endpoint" (paragraph bridging the left and right columns on page 43) and "Biomarkers require validation in most circumstances" (paragraph bridging pages 43-44).

Frank *et al.* (2003) *Nature Rev.* 2:566-580 concurs, stating, "The standard concepts of test-re-test reliability and validity apply with equal force to clinical biomarkers as they do in any assay system" and, "The work required to establish the reliability and validity of a new biomarker should not be underestimated in general, and in particular needs of planning for each combination of clinical indication and mechanism of action" (paragraph bridging the left and right columns on page 568). Feng *et al.* (2004) *Pharmacogenomics* 5:709-719 teaches, "The development and validation of clinically useful biomarkers from high-dimensional genomic and proteomic information pose great research challenges. Present bottle necks include: that few of the biomarkers showing promise in initial discovery were found to warrant subsequent validation…A molecular profiling approach, although promising, has a high chance of yielding biased results and overfitted models" (Abstract).

The unpredictability of correlating gene expression level to any phenotypic quality is also supported by the teachings of Wu (*J. Pathol.* **195**(1):53-65, 2001.). Wu teaches that gene expression data must be interpreted in the context of other biological knowledge, involving various types of "post genomics" informatics, including gene networks, gene pathways, and gene ontologies (page 53, left column). The reference indicates that many factors may be influential to the outcome of data analysis, and teaches that expression data can be interpreted in many ways. The conclusions that can be drawn from a given set of data depend heavily on the

particular choice of data analysis. Much of the data analysis depends on such low-level considerations as normalization and such basic assumptions as normality (page 63 – Discussion).

Additional post filing art reveals that most gene association studies are typically wrong. Lucentini (The Scientist, Vol. 18, page 20, 2004) teach that it strikingly common for follow-up studies to find gene-disease associations wrong (e.g. page 2, 1st paragraph). Lucentini teaches that two recent studies found that typically when a finding is first published linking a given gene to a complex disease there is only roughly a one-third chance that the study will reliably confirm the finding (e.g. page 2, 3rd paragraph). Lucentini teaches that bigger sample sizes and more family-based studies, along with revising statistical method, should be included in the gene association studies (e.g. page 3, 2nd paragraph).

In post-filing art, Barrier et al (*Oncogene* 24:6155-6164, 2005; IDS Ref) teach the attempted construction of a prognosis predictor model for stage II and stage III colon cancer based on gene expression measurements that involve a number of genes, but which do not involve the claimed panel of biomarkers (see entire document, especially pages 6156-6158). However, Barrier concedes that the results of the study only "suggest the possibility to build an accurate prognosis predictor using gene expression profiles" and that the study "has to be confirmed by larger other studies" (see page 6162, first full paragraph). In other post-filing art, Hao et al (*Clinical Cancer Research* **11**:1400-1407, 2005; IDS Ref.) teach that gene expression of the claimed sequences is altered in macroscopically normal colonic mucosa from individuals with a family history of sporadic colon cancer, but that prospective studies will be needed "to determine whether or not altered gene expression is associated with the subsequent development

of adenomatous polyps and/or colonic carcinomas" (see entire document, especially the Abstract).

The art teaches that gene expression analysis is commonly used for three different purposes: (1) as a screening tool to identify individual genes of interest that might contribute to an important biological function, (2) to obtain insight into an important biological function, and (3) as a classification tool to sort cases into clinically important categories (Pusztai and Hess, Annals of Oncology, Vol. 15, pages 1731-1737, 2004; e.g., paragraph bridging pages 1732-1733). In the instant case, the specification uses gene expression analysis to as a screening tool to identify genes of interest, and to obtain insight into an important biological function. However, the claims are drawn to using gene expression analysis to diagnose colorectal polyps and colorectal carcinoma. Pusztai and Hess teach that validation of gene expression important to biological function may be validated by using different methods, such as RT-PCR, whereas the most appropriate validation for using gene expression analysis as a classification tool is testing the predictor on independent sets of cases (e.g., page 1733, left column, 1st full paragraph). In the instant case the specification and declaration of Dr. Lee, filed 12/27/2007, provide an analysis by RT-PCR, but do not test the predictor on a set of cases.

Further, Shalon et al (US 2001/0051344 A1, Dec 13, 2001) teach that due to variations in genetic make-up of unrelated individuals in a heterogeneous society, differences in the expression of a gene between any two individuals may or may not be significant (e.g., paragraph [0155]). Shalon et al further teach that the larger the number of individuals tested, the more significant the remaining differences in gene expression become and samples from at least 5 and preferably 20-50 different test individuals are assayed to obtain statistically meaningful data

showing a statistical elevation or reduction in report levels when compared to control levels (e.g., paragraph [0156]). Pusztai and Hess teach that larger samples sizes may be needed to validate classification tests, and the number of samples will vary depending upon the acceptable error rates, level of inter-patient variability, the size of the difference in mean expression values, and the prevalence of the phenotype among the group being tested (e.g., page 1734, paragraph bridging columns; Table 1).

The prior art reveals that differences in gene expression observed between two groups are do not necessarily provide markers that can be used to reliably classify a subject. Golub et al (Science, Bol. 286, pages 531-537, October 1999) teach the use of a two-step procedure to test the validity of gene expression levels as predictors: step 1 involves cross-validation of the predictors on the initial data set, where one withholds a samples, builds a predictor based only on the remaining samples and predicts the class of the withheld sample; step 2 involves the repetition of assessing the clinical accuracy of the predictor set on an independent set of samples (e.g., page 532, right column). Although Golub et al could detect gene expression differences between chemotherapy responders and non-responders, those differences could not be use to predictably classify individuals (e.g., page 533, paragraph bridging left and middle columns). Accordingly, the art demonstrates the unpredictable nature of extrapolating gene expression differences to a method of class prediction.

Thus, the state of the art is underdeveloped with respect to the use of nucleic acids to diagnose and manage disorders in general; the state of the art is also underdeveloped with respect to the use of nucleic acids for the management of patient care and discovery of therapeutic interventions for CRC and colorectal polyps in particular.

Relative skill of those in the art and quantity of experimentation needed to make or use the invention: Although the level of skill in the art is high, one of ordinary skill would not be able to make and use the full scope of the invention now claimed and as asserted in the application without undue experimentation. The specification discloses a single panel of genes exhibiting altered expression in a mouse model comprising a chemically induced mutation in the APC gene and normal control littermates for which there was not aberration of the APC gene and analysis of a panel of six biomarkers applied to samples obtained from patients known to have CRC and from normal controls. The application also discloses differences in expression of three biomarkers in biopsy samples taken from one exemplary patient diagnosed with CRC.

Based on this disclosure, the application seeks to claim a method comprising measuring expression of any panel of biomarkers comprising any two polynucleotides selected from SEQ ID NO: 1, 2 and 5 expressed in a biological colorectal sample and comparing such expression levels to any control, wherein the comparison is determinative (i.e., diagnostic) of colorectal cancer and colorectal polyps and used in any aspect of the management of patient care in colorectal cancer and colorectal polyps, or such that the comparison is used in the discovery of any therapeutic intervention of colorectal cancer and colorectal polyps.

However, the art cited above clearly evidences that establishing expression of any single gene in any given cell system as a valid biomarker for any given condition is highly unpredictable and requires careful validation. This is acknowledged in the instant specification, which teaches that, "there is a distinct difference between research on a specific a gene, its expression, protein product, and regulation, and understanding what genes are critical to include in a panel used to for the analysis of CRC that is useful in the management of patient care for the

disease." (*Id.*) and that "given the complexity of biological systems, discovery of panels useful in providing value in patient care management for CRC is in the nascent stage" (*Id.*). In addition, as discussed above, the application teaches that there is substantial variation in expression levels of individual genes when compared with control sample (paragraph 0027), which necessitates the use of a panel of biomarkers for diagnostic validity.

Given the nascent and unpredictable state of the relevant art, one of ordinary skill would be required to empirically determine which panels of biomarkers and which biological samples within the expansive scope of the instant claims could be used to determine colorectal cancer and colorectal polyps in any given subject. Furthermore, one would be required to establish how RNA expression from genes of any given panel of biomarkers in any given biological sample correlates with any aspect of the management of patient care in colorectal cancer and colorectal polyps or with the therapeutic efficacy of an intervention. In view of the complex nature of the invention and the underdeveloped state of the art at the time of filing, which is acknowledged in Applicant's own specification, and the broad scope of the claims, there would be a large and prohibitive amount of experimentation required to make and use the claimed invention. Even for claims specifically reciting SEQ ID NOs: 1, 2, 5, 15 and 16 with particular samples from diseased tissue, one would have to establish that the differences in expression were statistically significant reliably correlated with the presence of colorectal cancer and polyps, risk assessment, prognosis and therapeutic effect. This would include analysis of the different levels of expression in a large number of individuals to establish the use of RNA expression levels of the claimed biomarkers as class predictors for colorectal polyps and colorectal carcinoma.

In view of the foregoing, the skilled artisan would not be able to make and use the invention presently claimed without first engaging in undue experimentation. Therefore, the claims are properly rejected under 35 USC § 112, first paragraph, as lacking an enabling disclosure.

Response to Arguments and the Declaration of Dr. Nancy M. Lee under 37 CFR §1.132

Declaration

The opinions expressed beginning in the paragraph numbered 6 on page 1 of the declaration through the first paragraph on the third page of the declaration pertain to the written description rejection. As the rejection was withdrawn in the prior action, those remarks will not be addressed herein.

Beginning in the second paragraph number 6 (page 3), the declaration describes experiments purported to establish a correlation between changes in expression of the SEQ ID NO: 1, 2 and 5 sequences and the presence of colorectal cancer and colorectal polyps. The data presented were obtained by rectal swab from normal appearing mucosa about 5-10 cm before the rectum of the subjects. RNA was isolated from the swab samples and RT-PCR'ed using the primers identified in the specification.

Validated controls were identified by determining the subject's family history and self history of cancer and the subject's own upper GI diseases and disorders. In addition, morphological identification of polyps and cancerous lesions identified during colonoscopy were also used to categorize subjects.

Marker expression was quantified (presumably by real time quantitative PCR although the declaration does not make this clear) and the data are analyzed by the □□CT method. The results, presented in Table 1, are characterized by Applicant as follows:

> Looking at Table I, for example, IL-8 in the control group has a ΔΔCT of 0.0050 and the cancer (PBS) group has a ΔΔCT of -3.191, an increase in IL-8 expression in the cancer group compared to control. As demonstrated by the data above, measuring at least two markers selected from IL-8, COX2 and SAA-1 provides information regarding the subject's disposition and development of polyps or cancer. (1) where an increase in IL-8 and COX2 is present in the subject compared to a control, the subject has or is at risk of having colorectal cancer or polyps; (2) where an increase in IL-8 and SAAl is present in the subject compared to a control, the subject has or is at risk of having colorectal cancer or polyps; (3) where an increase in COX-2 and SAAl is present in the subject compared to a control, the subject has or is at risk of having colorectal cancer or polyps; (4) where an increase in IL-8, COX2 and SAA1 is present in the subject compared to control the subject has or is at risk of having colorectal cancer or polyps; and (5) where an increase and then a decrease in SAAI is observed and an increase of IL-8 and/or COX2 is observed the subject had polyps and has transitioned to colorectal cancer. As indicated above, SAAl is a biphasic marker meaning that it changes during disease progression; however, SAA1 is elevated compared to control both at the polyp and cancer stages.

Declarant concludes that the data demonstrate that the measurement of any two biomarkers selected from IL-8, COX2 and SAA1 provide evidence of colorectal cancer or polyps in a subject when compared to controls as originally indicated, contemplated and claimed by the present application and currently claimed.

The Declaration under 37 CFR 1.132 is insufficient to overcome the rejection of claims 49, 51-55, 57, 58, 64, 79, 81-88 and 96-97 based upon insufficiency the disclosure under 35 USC § 112, first paragraph, as set forth herein above, in view of the evidence as a whole.

First, the showings of the declaration do not evidence enablement for the full scope of the claimed invention. The claims are drawn to the "determination of colorectal cancer and colorectal polyps." The "determination of colorectal cancer and colorectal polyps" is reasonably construed as diagnosis of colorectal cancer and colorectal polyps. Dependent claim 57 requires the use of the gene expression levels to identify a subject as a candidate for the management of colorectal cancer and colorectal polyps. To manage the polyps and cancer, one must be reliably diagnosed with the polyps and cancer. Dependent claim 58 indicates that the management of colorectal polyps and colorectal cancer encompasses risk assessment for unnamed events, early diagnosis, establishing prognosis, monitoring patient treatment for any treatment, and detecting relapse. The declaration does not demonstrate that applicant had enabled a method of diagnosis, for the management of colorectal polyps and colorectal carcinoma, including risk assessment, early diagnosis, establishing prognosis, monitoring patient treatment or detecting relapse.

The present specification teaches that the two criteria for assessing the effectiveness of biomarkers are selectivity and sensitivity, where selectivity refers to the percentage of patients correctly diagnosed, and sensitivity is defined as the probability that the disease is detected at a curable stage (e.g., paragraph [0014]). The specification teaches that there is a difference between diagnosis and risk assessment. The specification states the following at paragraph [0029]:

> The difference between risk assessment and early detection is the degree of certainty regarding acquiring CRC. Biomarkers that are used for early detection confer less than 100% certainty of CRC within a time interval, whereas biomarkers used for early detection confer an almost 100% certainty of the onset of the disease within a specified time interval.

The declaration provides a comparison between the mean expression levels of the biomarkers of SEQ ID NOs: 1, 2, 5, 15, and 16. The declaration does not provide evidence that the differences observed between the groups are sufficient to diagnose a subject with colorectal polyps and colorectal cancer.

The prior art reveals that differences in gene expression observed between two groups are do not necessarily provide markers that can be used to reliably classify a subject. Golub et al (Science, Bol. 286, pages 531-537, October 1999) teach the use of a two-step procedure to test the validity of gene expression levels as predictors: step 1 involves cross-validation of the predictors on the initial data set, where one withholds a samples, builds a predictor based only on the remaining samples and predicts the class of the withheld sample; step 2 involves the repetition of assessing the clinical accuracy of the predictor set on an independent set of samples (e.g., page 532, right column). Although Golub et al could detect gene expression differences between chemotherapy responders and non-responders, those differences could not be use to predictably classify individuals (e.g., page 533, paragraph bridging left and middle columns). Accordingly, the art demonstrates the unpredictable nature of extrapolating gene expression differences to a method of class prediction, which is required by the claims for the determination of colorectal polyps and colorectal cancer. Furthermore, the evidence presented does not demonstrate that Applicant had enabled methods of early diagnosis, establishing prognosis, monitoring patient treatment, and detecting relapse.

Further, the evidence presented in the declaration is not commensurate in scope with the claims encompass the use of a normal control sample from any tissue. The present specification

and declaration make use of only a colorectal biological sample. Thus, the claimed scope is broader that what is enabled.

The claims are drawn to the use of any two biomarkers selected from SEQ ID NOs: 1, 2 and 5, and further comprising any one of SEQ ID NOs: 15 and 16. In contrast, the Declaration states that the diagnosis of cancer and polyps is based on "an increase and then a decrease in SAA1 and an increase of IL-8 and/or COX2". Therefore, the Declaration evidences that determining colorectal cancer and polyps as recited in the instant claims is based on a biphasic response of SAA1. However, as this biphasic response is not disclosed in the instant application, the Declaration evidences that practicing the method as claimed requires information that was not disclosed in the application as of its filing date. Furthermore, the biomarkers of SEQ ID NOs: 15 and 16 also display a biphasic response. Therefore, the Declaration clearly evidences that the skilled artisan would not have been enabled by the specification to determine colorectal cancer and colorectal polyps at the time of filing using the claimed biomarkers. Given the lower standards applied to biomarkers for risk assessment, the data presented in the present specification and declaration indicate that increased RNA expression levels of SEQ ID NOs: 1 and 2 in a test colorectal sample as compared to a normal colorectal sample could be used to identify subjects at increased risk of colorectal polyps and colorectal cancer.

Thus, in view of the evidence considered as a whole, it is concluded that the Declaration fails to establish that one of skill in the art would have been enabled to make and use the invention presently claimed without undue experimentation.

Applicant Arguments

The rejection of claim 59 under 35 U.S.C. 112, first paragraph, is moot in view of Applicant's cancellation of the claim in the reply filed 10/22/2008.

With respect to the rejection of claims 49, 51-55, 57, 58, 60-64, 79, 81-88, 96 and 97 are rejected under 35 U.S.C. 112, first paragraph, Applicant's arguments filed 10/22/2008 have been fully considered but they are not persuasive.

At page 13, the response notes that methods of amplifying and quantifying mRNA expression levels were routine in the art at the time the invention was made, and thus the nature of the invention is not complex, as previously characterized by the Examiner. While these methods were routine in the art at the time the invention was made, the nature of the invention is complex in that it requires the use of the RNA expression levels for the determination of colorectal cancer and colorectal polyps and management of colorectal polyps and colorectal cancer, which encompasses risk assessment, early diagnosis, establishing prognosis, monitoring patient treatment, and detecting relapse. The use of RNA expression levels to reliably achieve these claimed outcomes is what makes the nature of the invention complex.

At the paragraph bridging pages 13-14, the response notes that the prior action indicated that the claims encompassed "any biological sample" and "any control" and the use in "any therapeutic intervention." The response asserts that Applicants have amended the claims to more clearly set forth the invention, including amending the claims to recite a "colorectal sample" with regard to the sample obtained from the test subject. The response asserts that one of ordinary skill in the art is capable of defining a control population/sample for purposes of the disclosure. The response asserts that one would know to measure and compare the expression level of a corresponding biomarker in a normal control sample. These arguments are not found persuasive.

The claims encompass the use of any biological sample for comparison purposes. The differences in gene expression used to "determine" colorectal cancer and colorectal polyps will vary based upon the level of gene expression in the control sample. For each different control sample, one would be required to experimentally determine the predictive ability of the method. This type of experimentation is not routine in the art. The area of the invention is unpredictable (e.g., see the above section titled *State of the prior art and level of predictability in the art*). Thus the experimentation required to identify appropriate control samples would be undue.

At page 14, the response asserts that the claimed method can be used to manage patient care, because a difference in a biomarker expression level compared to a control "identifies a subject as a candidate for the management of colorectal cancer…" as stated in claim 57. The response asserts that this phrase means that aberrant expression levels should be further monitored, tested or otherwise "managed" for risks of colorectal cancer and polyps. These arguments are not found persuasive. The claim does not state that the subject should be managed for risk of colorectal cancer. As written, the claim reads upon the management of the treatment of subjects diagnosed with colorectal polyps and colorectal cancer, yet Applicant has not enabled the claimed method for diagnosis of colorectal cancer for the reasons discussed in the above rejection and the section in response to the declaration of Dr. Lee, filed 12/27/2007.

At page 14, the response notes that the claimed invention is not directed to the measurement of protein expression levels. This argument has been found persuasive, and the comments regarding protein expression have been removed from the rejection.

At the paragraph bridging pages 14-15, the response asserts that data obtained and published in peer reviewed journals support Applicant's claimed invention post-filing. The

response cites Hao et al. Clin Cancer Res. 2005 15:11(4):1400-7, also cited on the IDS filed 3/6/2006. Further, the response points to the declaration of Dr. Nancy Lee in support of the claimed invention. The evidence presented in Hao et al and the declaration is not commensurate in scope with the claims. See the section above for a discussion of the declaration of Dr. Nancy Lee. Hao et al teach the range and mean ± standard deviation of IL-8, COX-2, SAA1 and PPAR-alpha expression in normal colon and in the colons of subjects with a family history of colorectal carcinoma (e.g., Table 2). Although differences in gene expression were observed, those differences are not specifically correlated with the future development or presence of colorectal polyps or colorectal carcinoma. Hao et al state the following at page 1406, right column:

> Because the genes analyzed in this study are involved in the development of colon cancer, we hypothesize that individuals with altered gene expression in the MNCM may be more susceptible to developing polyps or cancer than those without altered gene expression. To test this hypothesis, a prospective study with a larger number of study subjects will be needed. If such an association is confirmed, it may be possible to identify individuals at increased risk of developing colon cancer by using gene expression analysis of rectosigmoid biopsy samples. Theoretically, it is easier to identify individuals with global alterations in the MNCM than individuals with local alterations by analysis of random MNCM samples. However, if an appropriate panel of genes was selected for analysis using multiple samples, it may have enough predictive power to identify such patients.

Thus, the experimental data presented by Hao et al is insufficient to enable the presently claimed invention. Further experimentation would be required to determine how to use the gene expression levels of all of the claimed combination of genes for the diagnosis of colorectal polyps and colorectal cancer and the management, which includes risk assessment, early diagnosis, prognosis, monitoring patient treatment and detecting relapse.

At pages 15-16, the response notes that it is not the place of the PTO to require the data necessary for FDA submissions. The response asserts that "the question for the PTO is whether the inventive concept is satisfied by the specification and claims." The response asserts that the Office is asking for more data in addition to (i) the animal model of the specification, (ii) the colorectal cancer patient data of the specification, and in addition to (iii) the 92 normal subject, 148 subjects with family history/self history, 100 patients with polyps and the at least 50 patients with cancer set forth in the 1.132 declaration. The response asserts that the data demonstrate the claimed invention. The response asserts that the declaration of Dr. Lee provides validation of the claimed biomarkers. These arguments are not found persuasive. The question for the PTO is whether the specification describes the invention in such terms that one skilled in the art can make and use the claimed invention to ensure that the invention is communicated to the interested public in a meaningful way. The information contained in the disclosure of an application must be sufficient to inform those skilled in the relevant art how to both make and use the claimed invention. In the instant case, the full scope of the claimed invention is not enabled by the present specification and knowledge that one of skill in the art would have had at the time the invention was made. Applicant may provide evidence to support enablement of the claimed invention at the time the invention was made. Applicant has not provided any data with regard to the classification of individuals as having or not having colorectal polyps and colorectal cancer based upon the level of RNA expression of two biomarkers selected from SEQ ID NOs: 1, 2 and 5, with or without the addition of the biomarkers of SEQ ID NOs: 15 and 16. The data presented shown differences in expression between two patients or groups of patients; however, the prior art teaches that differences in gene expression do not always indicate that the gene can

be used to classify individuals (Golub et al, 1999). No data has been provided to enable management of colorectal cancer and colorectal polyps, including risk assessment, early diagnosis, establishing prognosis, monitoring patient treatment, or detecting relapse.

At pages 15-16, the response asserts that the specification and declaration by Dr. Lee indicate that (i) measuring expression levels of the at least two polynucleotides in colorectal samples is associated with colorectal cancer or polyps (including the markers of SEQ ID NOs: 1, 2 and 5), (ii) because the claims recite "comprising," other markers can be used in addition to the claimed markers, and that (iii) the technique for measuring RNA expression are useful in the methods of the disclosure. Even if the levels of expression are "associated" with colorectal polyps or cancer, the claims require the use of the gene expression levels as a class predictor to manage colorectal cancer and colorectal polyps, provide early diagnosis, establish a prognosis, monitor treatment, and detect relapse. A mere association is not sufficient to accomplish each of these outcomes. See the discussion in the above section titled *State of the prior art and level of predictability in the art.* If other markers are critical to the success of the claimed invention, they must be specifically recited in the claims. It would require undue experimentation to randomly screen other markers that could be encompassed by the claimed to identify markers that enable the claimed invention. Even if methods of measuring RNA expression are routine in the art, the claims are not limited to merely measuring RNA expression levels. The claims require the use of the RNA expression levels to diagnose and manage colorectal polyps and colorectal cancer.

At pages 16-17, the response asserts that any experimentation required to practice the claimed invention would not be undue in light of the specification and high skill in the art, and

the demonstrated success and confirmation of the disclosure in Dr. Lee's 1.132 declaration. The response asserts that any experimentation required would be routine experimentation. These arguments have been fully considered but are not persuasive in view of the record as a whole. As described above, the evidence presented in the Declaration does not show enablement for the full scope of the claimed invention and actually demonstrates that determination of colorectal cancer and colorectal polyps requires knowledge of the biphasic nature of SAA-1, PPAR-alpha, and PPAR-gamma expression, which is not disclosed in the instant application. Clearly, given the highly unpredictable state of the art, the claims are not enabled for such expansive scope. In addition, no guidance is provided with regard to how to obtain outcomes such as "establishing prognosis" and "discovery of therapeutic intervention" as recited in the claims.

At pages 17-18, the response notes that the prior action contained comments that related to the claims being constructed such that the measured expression did not require the use of the recited biomarkers. Applicant has amended the claims to require the recited biomarkers.

Thus, in view of the scope of the claims, the unpredictable state of the art, and the failure of the application to provide information critical to practicing the invention as claimed, one of skill in the art would not have been able to make and use the claimed invention without undue experimentation.

Response to Arguments - 35 USC § 102

The rejection of claims 79, 81-83, 86, 87 and 88 under 35 U.S.C. 102(b) as being anticipated by TaqMan® EZ RT-PCR kit Protocol, Applied Biosystems, Printed in the USA,

4/2002, has been withdrawn in view of Applicant's amendment to the claims in the reply filed 10/22/2008.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 79 and 81-87 are rejected under 35 U.S.C. 103(a) as being unpatentable over Baker et al (WO 2003/078662 A1; see the entire reference) in view of Gould et al (Kidney International, Vol. 61, pages 51-60, January 2002; see the entire reference), Goltry et al. (US Patent No. 6,025,336; see the entire reference), GenBank Accession No. M23698 (GI: 758678, publicly available April 1995; see the entire reference), Buck et al (Biotechniques, Vol. 27, No. 3, pages 528-536, 1999, cited on the IDS filed 4/2/2007; see the entire reference), and Ahern et

al (The Scientist, Vol. 9, Issue 15, page 20, July 1995; see the entire reference). This is a new rejection.

Claim 79 is drawn to a kit comprising at least one reagent, which is oligonucleotides comprising the sequences set forth in SEQ ID NO: 45, 46, 47, 48, 53 and 54; and instructions for using the kit for analyzing polynucleotide expression levels. The preamble of the claim merely recites the purpose of a process and the intended use, and the body of the claim does not depend on the preamble for completeness. The structural limitations of the body of the claim are able to stand alone. Claims 81-83 further modify the preamble of the claim and content of instructions. Claim 84 is limits the oligonucleotides to at least two sets of primers chosen from (i) SEQ ID NO: 45 and 46; (ii) SEQ ID NO: 47 and 48; (iii) SEQ ID NO: 53 and 54; (iv) SEQ ID NO: 73 and 74); and (v) SEQ ID NO: 75 and 76 (i.e., at least two sets of primers that consist of the recited sequences). Claim 85 further requires reagents for the preparation of cDNA. Claim 86 further requires a reagent that is used for detection and quantification of polynucleotides. Claim 87 limits the reagent to one that includes at least one chromophore.

Baker et al teach a panel of two or more gene specific primers selected from the group consisting of the forward and reverse primers listed in Table 2 (e.g., page 18, lines 3-4). Table 2 contains forward and reverse primers for COX2 (PTGS2), which consist of SEQ ID NOs: 229 and 230 (e.g., Table 2 at page 72). The sequences of Barker et al, SEQ ID NOs: 229 and 230 consist of sequences 100% identical to the claimed sequences of SEQ ID NOs: 47 and 48 (see the attached alignments in Exhibits I and II). Baker et al teach that the primers may be used for gene expression profiling using RT-PCR preceded by an amplification step (e.g., page 5, lines 22-27; page 7, lines 7-9 and 25). Further, Baker et al teach RT-PCR of IL8 (e.g., page 8, lines

31-33). Baker et al teach further reagents for RT-PCR, including reagents for the preparation of cDNA, such as the GeneAmp RNA PCR kit; and reagents for the detection and quantitation of polynucleotides that contain at least one chromophore, such as components for TaqMan PCR® where the probe is designed to detect a nucleotide sequence between the two primers and is labeled with a reporter fluorescent dye (e.g., pages 31-32). Baker et al teach that RT-PCR is a flexible and quantitative method that can be used to compare mRNA levels in different sample populations, in normal and tumor tissues (e.g., breast cancer) to characterize patters of gene expression (e.g., page 31, lines 8-11).

Baker et al do not teach oligonucleotides to amplify the IL8 mRNA that consist of instant SEQ ID NOs: 45 and 46 and do not teach oligonucleotides comprising SEQ ID NOs: 53 and 54 (sequences of SAA1). Further, Baker et al do not specifically teach the components in kit form with instructions.

Gould et al teach oligonucleotides to be used as primers for RT-PCR of IL8 (e.g., Table 1). The forward primer for IL8 is 5'-AGATATTGCACGGGAGAATATACAAA-3', and the reverse primer for IL8 is 5'-TCAATTCCTGAAATTAAAGTTCGGATA-3' (Table 1). The primer sequences taught by Gould et al, consist of a nucleic acid sequence 100% to SEQ ID NOs: 45 and 46.

Goltry et al teach that specific oligonucleotide primers are generated for SAA1 to perform RT-PCR in samples, including samples obtained from patients who have been exposed to ionizing radiation for the treatment of solid tumors such as breast cancer (e.g., column 6, lines 22-43). Goltry et al teach a kit comprising primers specific for a particular gene or gene fragment, reagents for RT-PCR analysis, and instructions for using the primers and the reagents

in an assay (e.g., paragraph bridging columns 6-7). Goltry et al teach a primer that consists of the human SAA1 sequence of CTCGGGACATGTGGAGAGCCTACTCTATTAGATACCCATTGTGTACCCTCT (e.g., Table 4), which comprises the sequence of instant SEQ ID NO: 53 (underlined portion).

GenBank Accession No. M23698 teaches the sequence of the human serum amyloid A1 (SAA1) mRNA, which comprises instant SEQ ID NOs: 53 and 54.

Buck expressly provides evidence of the equivalence of primers. Specifically, Buck invited primer submissions from a number of labs (39) (e.g., page 532, column 3), with 69 different primers being submitted (e.g., page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18-mer primers on the 300 base pair sequence (e.g., page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that every single primer worked (e.g., page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, every single control primer functioned as well (e.g., page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (e.g., page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

Ahern et al teach that packaging reagents in kit format is convenient, offering the scientists the opportunity to better manage their time. Ahern et al teach that premade reagents and packaged kits, including detailed instructions, saves researchers time (e.g., pages 4/5-5/5).

Because both Baker et al and Gould et al teach primers for RT-PCR of IL8, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the specific IL8 primers of Gould et al for the unspecified IL8 primers of Baker et al in order to achieve the predictable result of providing primers for the amplification of IL8 cDNA obtained from mRNA. One would have been motivated to use the primers of Grould et al, because they were shown in the art to perform such a function. The primers of Gould et al consist of instant SEQ ID NOs: 45 and 46.

Because both Baker et al and Goltry et al teach providing primers for RT-PCR of mRNA obtained from breast cancer subjects, it would have been obvious to one of ordinary skill in the art to include primers for amplification of SAA1, as taught by Goltry et al. One would have specifically included the disclosed forward primer of Goltry et al (comprising instant SEQ ID NO: 53). Further, it would have been obvious to one of ordinary skill in the art at the time the invention was made to further include a reverse primer for SAA1, because Baker et al teach RT-PCR with a forward primer and reverse primer. To provide such a reverse primer, the skilled artisan would have looked to the known SAA1 mRNA sequence taught by GenBank Accession No. M23698, which comprises both instant SEQ ID NOs: 53 and 54. The prior art is replete with guidance and information necessary to permit the ordinary artisan in the field of nucleic acid detection to primers for PCR. The ordinary artisan would be motivated to have designed and tested new primers or probes to obtain additional oligonucleotides that function to amplify

SAA1, including primers comprising instant SEQ ID NO: 54. Moreover, it would have been obvious to one of skill in the art to combine the primers and reagents in kit form with instructions, because Baker et al, and Goltry et al teach reagents for RT-PCR in kit form, and Ahern et al teach that kits including detailed instructions saves researchers time.

One would have been motivated to make such modifications in order to receive the expected benefit of expanding the repertoire of primers available to perform RT-PCR and to provide such reagents in a form that saves time as taught by Ahern et al. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claim 88 is rejected under 35 U.S.C. 103(a) as being unpatentable over Baker et al (WO 2003/078662 A1; see the entire reference) in view of Gould et al (Kidney International, Vol. 61, pages 51-60, January 2002; see the entire reference), Goltry et al. (US Patent No. 6,025,336; see the entire reference), GenBank Accession No. M23698 (GI: 758678, publicly available April 1995; see the entire reference), Buck et al (Biotechniques, Vol. 27, No. 3, pages 528-536, 1999, cited on the IDS filed 4/2/2007; see the entire reference), and Ahern et al (The Scientist, Vol. 9, Issue 15, page 20, July 1995; see the entire reference) as applied to claims 79 and 81-87 above, and further in view of Qiagen News (Issue 2, pages 1-13, 1998; see the entire reference). This is a new rejection.

The teachings of Baker et al, Gould et al, Goltry et al, GenBank Accession No. M23698, Buck et al, and Ahern et al are described above and applied as before. Further, Baker et al teach the use of RNeasy™ Mini kit for RNA isolation for use in RT-PCR.

Baker et al, Gould et al, Goltry et al, GenBank Accession No. M23698, Buck et al, and Ahern et al do not explicitly teach labware for at least one of sample collection, sample preparation or sample analysis.

Qiagen News teaches RNeasy Mini Kits comprising RNeasy mini spin columns, collection tubes, and RNase-free reagents and buffers (e.g., page 13). Further, Qiagen News teaches that RNeasy can be used for the synthesis of high quality cDNA from RNA isolated from breast tumor biopsy tissue (e.g.., page 12).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify combined the teachings of Baker et al, Gould et al, Goltry et al, GenBank Accession No. M23698, Buck et al, and Ahern et al to include the RNeasy kit components including labware from sample preparation taught by Qiagen News because Baker et al teach it is within the ordinary skill in the art to use RNeasy for sample preparation and Qiagen News teach the RNeasy kit components.

One would have been motivated to make such a modification in order to receive the expected benefit of providing reagents capable of high quality cDNA from tissues of interest including breast tumor biopsy tissue as taught by Qiagen News. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached at 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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